Modeling the Toxicokinetics of Multiple Metals in the Oyster *Crassostrea hongkongensis* in a Dynamic Estuarine Environment

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S *Supporting Information*

ABSTRACT: Metal contamination is a major problem in many estuaries. Toxicokinetic models are useful tools for predicting metal accumulation in estuarine organisms and managing the associated ecological risks. However, obtaining toxicokinetic parameter values with sufficient predictive power is challenging for dynamic estuarine waters. In this study, we determined the toxicokinetics of multiple metals in the oyster *Crassostrea hongkongensis* in a dynamic estuary polluted by metals using a 48 day transplant experiment. During the experiment, metal concentrations in oysters, water, and suspended particles were intensively monitored at 3 day intervals. The toxicokinetic parameters were then estimated using the Markov chain Monte Carlo (MCMC) method. The calibrated model was capable of successfully simulating the time-course of metal bioaccumulation in oysters and was further validated by predicting the bioaccumulation at another site in the estuary. Furthermore, the model was used to assess the relative importance of different pathways in metal bioaccumulation. With the MCMC method, distributions instead of single values were assigned to model parameters. This method makes the model predictions probabilistic with clearly defined uncertainties, and they are thus particularly useful for the risk assessment of metals in aquatic systems.
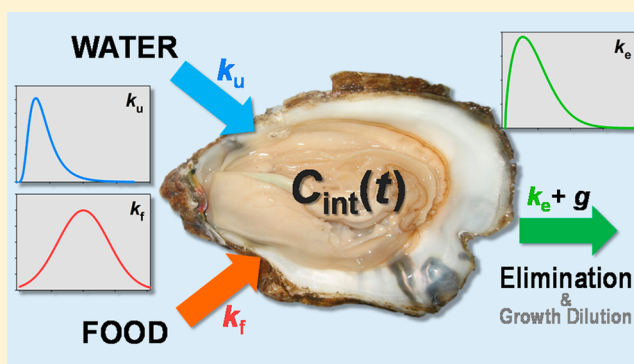
INTRODUCTION

In aquatic environments, the relationship between metal bioaccumulation by aquatic organisms and the environmental exposure (dissolved and particulate metals) is complex and dependent on a myriad of biotic and abiotic factors.[1] Quantifying the relationship is important for interpreting biomonitoring data in relation to the levels of contamination.[2−4] Hypothetically, when equilibrium partitioning of metals is attained between organisms and environmental compartments (e.g., water, suspended particles, and sediments), a simple bioconcentration factor can adequately measure the aforementioned relationship.[5] However, reaching such an equilibrium requires long-term exposure under stable conditions, including metal concentrations and physicochemical and biological factors affecting bioavailability. Therefore, such an equilibrium in real aquatic environments is rare if not impossible. To better understand bioaccumulation in variable or dynamic aquatic environments, such as riverine and estuarine waters, kinetic measures are often required.[5−7]

A good toxicokinetic model should be sufficiently sophisticated for simulating the major bioaccumulation processes but simple enough for convenient application. The one-compartment first-order toxicokinetic model meets both criteria. The model is simple, with only four to five parameters, and yet considers processes including aqueous uptake, dietary

uptake, elimination, and growth dilution.[5,8,9] This model is also known as the biokinetic or biodynamic model in the area of metal ecotoxicological studies; the parameter values are usually derived in laboratories under stable conditions.[8,9] Such laboratory-derived parameters have been tested in a number of previous studies for predicting metal bioaccumulation in the field and have shown good predictive powers.[8,10−12] Nonetheless, less-precise predictions are also reported in some studies.[11,13]

Applying parameters calibrated under constant laboratory conditions to dynamic estuarine waters is more challenging. In the case of unsatisfactory prediction, the model parameters need to be updated with the field data in a scientifically sound way; otherwise, the newly obtained biomonitoring data would not contribute to the enhancement of the model's predictive power and be missed. Moreover, although the toxicokinetic model is kinetic in nature, previous studies seldom used the model in its kinetic form for predicting the time-course metal bioaccumulation.[8,10,11] Instead, the steady-state concentration in organisms was calculated by assuming a constant exposure

for predicting metal bioaccumulation in the field. This practice does not fully explore the predictive power of the toxicokinetic model and may not be appropriate in dynamic environments (e.g., estuaries) in which steady-state or constant exposure is not possible.

In this study, we transplanted the oyster (*Crassostrea hongkongensis*) to a region of Jiulong River estuary significantly contaminated by multiple metals. Our objective was to calibrate and validate the toxicokinetics of multiple metals simultaneously in a real estuarine environment. The parameter values reported in the literature were used as prior information. During the 48 day oyster transplant, the diffusive gradients in thin films (DGT) technique was used for measuring labile metal concentrations in water. Metal concentrations in suspended particles were also measured periodically to reflect the dietborne exposure. The bioaccumulation of metals in oysters were subsequently simulated with the one-compartment first-order toxicokinetic model using metal concentrations in water and suspended particles as driving variables. The Markov chain Monte Carlo (MCMC) method was used for parameter fittings to provide distributions of parameters and better uncertainty analysis.

■ MATERIALS AND METHODS

Study Area. The two sites for oyster transplant were in the north arm of the Jiulong River estuary (Figure S1), which is close to Xiamen City in the southeast of China and has a subtropical climate. Site 1 was directly affected by the effluent discharged from Huyu floodgate; site 2 was approximately 2 km downstream (see Figure S1 for the map). Upstream of Huyu floodgate is a drainage canal that receives both domestic and industrial wastewater from Jiaomei Town. Levels of multiple metals are high in the canal. The wastewater was discharged into Jiulong River estuary during low tides irregularly, but they are, on average, every 2 to 3 days. The wastewater discharge substantially elevated the metal concentrations in the estuarine water nearby. The average concentrations of dissolved Cr, Ni, Cu, and Zn measured recently by Wang and Wang during their two sampling events were around 10, 30, 10, and 10 μg L^{-1}, respectively,[7] which were similar to those reported by Weng and Wang earlier.[14]

Oyster Transplant and Sampling. The 48 day oyster transplant experiment was conducted between November 16th, 2013 and January 3rd, 2014. The oysters were juvenile (2−3 months old) *C. hongkongensis* collected from an oyster farm in Jiuzhen Harbour (24°2′15″ N, 117°42′44″ E), where no obvious metal contamination was detected.[14] At each site, around 300 oysters were placed in a mesh bag that was then fastened to a bamboo pole. The bamboo pole was inserted firmly into the sediment to keep the oysters suspended under water during the whole tidal cycles. Losses of oysters due to mortality or other causes were not counted but were estimated to be minimal. Of the ~300 oysters transplanted, 170 were sampled for metal analyses, 85 were sampled for determining metal subcellular distribution (results not presented in this study), and the others were discarded.

Samples of 10 oysters were collected at 3-d intervals from each site. Oyster shells were washed with on-site water to remove sediments. The oysters were then placed in clean zipper-lock bags and transported to the laboratory in an icebox immediately. In the laboratory, the oysters were opened with a stainless steel oyster knife. The soft parts were thoroughly rinsed with deionized water to remove any visible sediment

particles, dried at 80 °C for 48 h, and weighed. The oysters were not depurated, following the methods commonly used by environmental authorities in biomonitoring programs, e.g., the marine monitoring programs in China and the mussel watch program in the United States.[15,16] The measured bioaccumulated concentrations of some metals may thus include contributions from gut content due to the higher concentrations of these metals in the particulate phases than in the oysters,[17] but this was considered negligible by theoretical calculation.[18] The oyster tissues were digested with concentrated HNO$_3$ in 15 mL polyethylene tubes. A total of 2 mL of 65% HNO$_3$ was added to each tube, and tubes were left at room temperature for 8−12 h until most solids were dissolved. The tubes were further heated at 80 °C for 8 h using a dry block heater. After heating, the liquids became clear with some lipid precipitates in the bottom of the tubes. The standard reference material SRM1566b (oyster tissue) was digested together with each batch of the samples.

Samples of Water and Suspended Particles. Water samples were collected each time with the oyster sampling. A total of three replicates of 500 mL of water were taken using polyethylene bottles by immersing them in the water at a depth of around 10 cm with nitrile-gloved hands. The bottles were previously acid washed (soaked in 5% HNO$_3$ for at least 24 h) and rinsed 6 times with deionized water and were placed in double zipper-locked bags before use. The bottles were rinsed with site water three times before collecting water samples.

In the laboratory, the salinity of the water samples was measured with a salinity refractometer (Suwei LS10T); pH and temperature were measured with a benchtop pH meter (pH 510, EUTECH). Each water sample was filtered through a preweighed 0.45 μm polycarbonate filter for analyzing the particulate metals. The filters were dried at 80 °C for 48 h and weighed. Each filter together with the particles were digested in a mixture of 4.5 mL of 65% HNO$_3$ and 1.5 mL of 35% HCl using a microwave digestor (Preekem Coolpex). The temperature program was 3 min at 150 °C, 180 and 200 °C, respectively, with another 30 min at 220 °C. The digested samples were centrifuged at 3000g for 5 min, and the supernatants were decanted into new polyethylene tubes for metal concentration analysis. A total of three blank filters and the standard reference material (coastal sediment, GBW07314) were also digested with each batch of samples and served as procedure blanks and quality control samples, respectively.

DGT Measurement. The DGT technique was used for measuring labile metal concentrations in water. The DGT probes were purchased from DGT Research Ltd. (Lancaster, UK). A DGT probe was deployed at each site every 3 days during the oyster transplant experiment following the method described by Dunn et al. and was retrieved ~3 days later.[19] The exact time of DGT deployment and the average temperature during the period of deployment were recorded. In the laboratory, the retrieved DGT probes were first cleaned with deionized water and then dissembled. The Chelex gel layer was placed in a 2 mL centrifuge tube using acid-washed plastic forceps and was eluted with 1 mL of 1 mol L^{-1} HNO$_3$ for 24 h. Metal concentrations in the eluent were determined after appropriate dilution. Labile metal concentrations in water were calculated using the equation and diffusion coefficients provided by the DGT manufacturer (see the Supporting Information for more details). Time-integrated average metal

concentrations during every 3 days were expected to be provided by this method.

Metal Concentration analysis. Metal concentrations in samples of oyster, suspended particles and DGT eluents were determined using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700x). The internal standards, including [45]Sc, [72]Ge, [115]In, and [209]Bi, were used for correcting instrument drift and matrix effects. A quality control sample was measured every 10 samples. For the standard reference material GBW07314, the recovery of Co, Ni, Cu, Zn, and Cd was in the range of 90% to 110%, whereas the average recovery of Cr and Pb were 80% and 84%, respectively. The lower recoveries of the two metals were probably due to the pseudototal (instead of the total) digestion method that we used. The recoveries of all metals from the standard reference material SRM1566b were within the range of 90 to 108%. The reported metal concentrations were thus not corrected for recoveries.

Toxicokinetic Modeling. Both water and food are potential sources of metals for the oysters. By assuming first-order kinetics for the uptake and elimination processes, the time-course of metal concentration in oysters can be described by a one-compartment toxicokinetic model:[8,9]

$$\frac{dC_{int}(t)}{dt} = k_u \cdot C_w(t) + k_f \cdot C_f(t) - (k_e + g) \cdot C_{int}(t) \tag{1}$$

where $C_{int}(t)$ is the metal concentration in oysters ($\mu g\ g^{-1}$ dry weight); $C_w(t)$ is the concentration of dissolved metals ($\mu g\ L^{-1}$), which was measured using the DGT technique in this study; $C_f(t)$ is the metal concentration in food particles ingested by oysters ($\mu g\ g^{-1}$); k_u is the uptake rate constant of dissolved metals ($L\ g^{-1}\ day^{-1}$); k_f is the uptake rate constant of metal from food ($g\ g^{-1}\ day^{-1}$); k_e is the elimination rate constant (day^{-1}); g is the growth rate constant (day^{-1}); and t is the time of exposure (day). The parameter k_f can be considered as the product of ingestion rate (IR, $g\ g^{-1}\ day^{-1}$) and assimilation efficiency (AE, dimensionless) described in previous studies.[8,9] In the present study, it is difficult to estimate IR and AE separately; k_f is thus used for simplicity and practicality.

Parameter Estimation and Model Prediction. The growth rate constant (g) was estimated based on the increases of individual dry weight of oysters at each site (Figure S2). The values of g were subsequently kept fixed during the estimation of the other three parameters, i.e., k_u, k_f, and k_e, for each metal. The parameters were estimated using bioaccumulation data collected from site 1, while the data of site 2 were used to validate the model.

The parameters were estimated following the procedures proposed by Ashauer et al.[20] First, least-squares fittings with the Marquardt algorithm were used to find the parameter values that minimize the sum of the squared residuals. The starting parameter values were set based on the literature on metal toxicokinetics (or wherein called biokinetics) in oysters and are listed in Table S1.[21−24] Subsequently, MCMC fittings with the Metropolis−Hastings algorithm were applied to the bioaccumulation data to generate parameter samples of k_u, k_f, and k_e. The best-fit values from the least-squares fittings were used as priors for the MCMC fittings. Uniform distributions, with the lower and higher bound at 0.1 fold and 10-fold of the best-fit values, were used as the prior distributions (see Table S2). A parameter sample is a large number of accepted parameter combinations from which correlation among

parameters can also be inferred (see Figure S7−S13 for examples).[25] The parameter sample thus can be considered as a joint posterior distribution of the model parameters. The parameter samples were further used to generate predictions of metal bioaccumulation in the oysters and the 95% confidence intervals. All of the model fittings and predictions were conducted with the software openmodel (version 2.4.2) developed by Neil Crout of the University of Nottingham.

■ RESULTS AND DISCUSSION

Physicochemical Parameters. The salinity of water samples varied markedly from 3 to 15 and 5 to 22 at the site 1 and 2, respectively (Figure S3). Higher salinity was observed at site 2, which was closer to the sea end. Similarly, pH values also varied substantially. Most of the measured pH were relatively low and ranged from 6.5 to 7.5. The low and even acidic pH values were probably caused by the wastewater discharge from the Huyu floodgate. The salinity and pH were measured in grab samples taken at different tidal phases (but usually during low waters) on different days; the observed variations were thus the result of the combined effect of spring−neap and low−high tide cycles.

The tide is semidiurnal in the Jiulong River estuary. Salinity and pH were usually higher at high tides. For example, adjacent to the sites of this study, it was recorded that salinity increased from ∼5 at low tides to ∼25 at high tides; in the meantime, pH increased from 7.0 to 7.4 to 7.6−7.8.[7] The concentrations of dissolved organic carbon (DOC) also varied with tide and increased from around 0.3 mM C at high tides to more than 2 mM C at low tides.[7] The bioavailability of metals is determined by multiple variables, including salinity, pH, and DOC; therefore, metal bioaccumulation rates in waters with dynamic water chemistry, such as Jiulong River estuary, are expected to vary with time in a very complex way even if metal concentrations are stable.

Metal Concentrations in Water and Suspended Particles. Metal concentrations in water (measured by DGT probes) and suspended particles also varied considerably during the 48 d of oyster transplant (Figures 1 and 2). The patterns of variation were similar for the two study sites, driven by both tidal mixing and wastewater drainage. For the particulate metals, similar patterns were observed among different metals (i.e., Cr, Ni, Cu, and Zn), suggesting the same source of contamination (Figures 2 and S5). The elevated levels of Cr, Ni, Cu, and Zn in Jiulong River estuary and the concurrence of these metals were also previously reported.[26] In contrast, the correlations among metals in water were relatively weak (Figure S4).

Dissolved Metal. The concentrations of dissolved metals measured by DGT probes are summarized in Figure 1. The DGT technique provides time-integrated concentrations of labile metals during the consecutive deployment periods of around 3 days each. Metal concentrations were generally higher at site 1, which was closer to the floodgate, than at site 2. Compared to other clean or contaminated estuaries (Table S4), the study sites were subjected to significant contamination of Ni (site 1:10−61 $\mu g\ L^{-1}$; site 2:6−35 $\mu g\ L^{-1}$), Cu (site 1: 3−53 $\mu g\ L^{-1}$; site 2: 2−19 $\mu g\ L^{-1}$) and Zn (site 1: 7−35 $\mu g\ L^{-1}$; site 2: 4−34 $\mu g\ L^{-1}$). The concentrations of Co, Cd, and Pb were slightly elevated but were still at relatively low levels (Figure 1 and Table S4). The measured Cr concentrations were quite low (site 1:0.54 ± 0.43 $\mu g\ L^{-1}$; site 2: 0.30 ± 0.28 $\mu g\ L^{-1}$); however, it should not be interpreted as low Cr
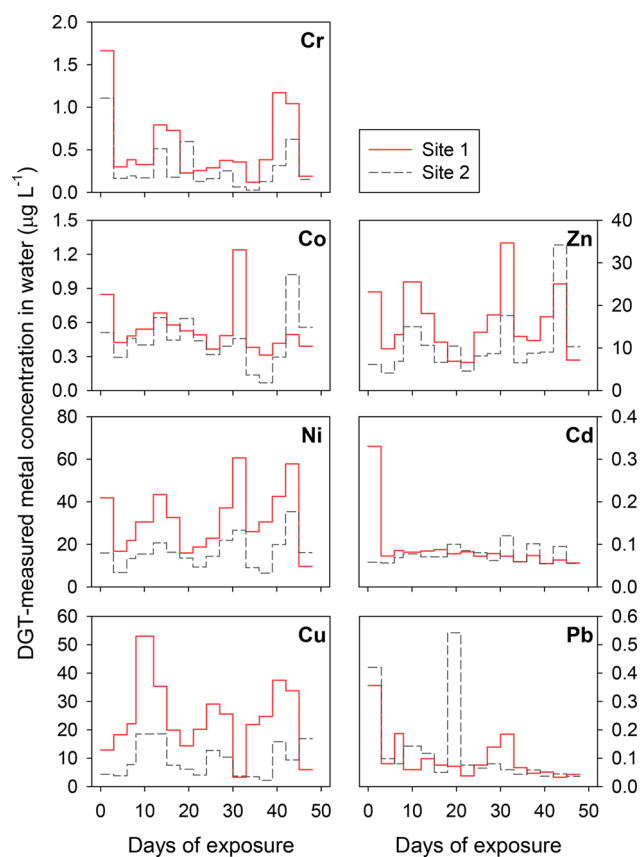
Figure 1. Labile metal concentrations in water measured at ~3 day intervals using DGT probes at the two study sites during the 48 day oyster transplantation.

Figure 2. Metal concentrations in suspended particles collected at the two study sites during the 48 day oyster transplantation. Values are mean ± standard deviation (n = 3).

contamination in this area but rather due to the DGT technique (see the discussion below). In actuality, noticeably high Cr concentrations ($2-18 \mu g\ L^{-1}$) were detected in the 0.2 μm filtered water samples by Wang and Wang near the study sites during two independent sampling events.[7]

The DGT probes used in this study measured only the fraction of dissolved metal species that are potentially more bioavailable. In theory, they are cationic species that can bind to Chelex resin, including free metal ions, simple inorganic complexes, and small organically complexed species.[19] Therefore, the DGT-reactive proportion is metal-specific and dependent on the conditions of water. In a study of estuarine waters, the DGT-reactive metal concentrations as a fraction of 0.45 μm filterable concentrations was 21 ± 2% for Cu, 29 ± 11% for Pb, 28 ± 5% for Zn, and 27 ± 12% for Ni.[19] In another study of near-pristine coastal waters, the ratio of DGT-reactive to 0.45 mm filterable concentrations was 51% for Cu, 108% for Cd, 104% for Co, and 122% for Pb.[27] The Cr species measured by the DGT probes were cationic species (e.g., Cr^{3+} and $Cr(OH)_2^+$), whereas the dominant species of Cr in estuarine waters was Cr(VI) anionic species. For example, in the Columbia River and estuary, CrO_4^{2-} was found to account for more than 90% of the dissolved Cr; Cr(III) species had strong tendency of particle adsorption, which limited their availability as dissolved species.[28] This explained why in this study Cr concentrations measured in DGT probes were 1 to 2 orders of magnitude lower than the concentrations of filterable Cr.
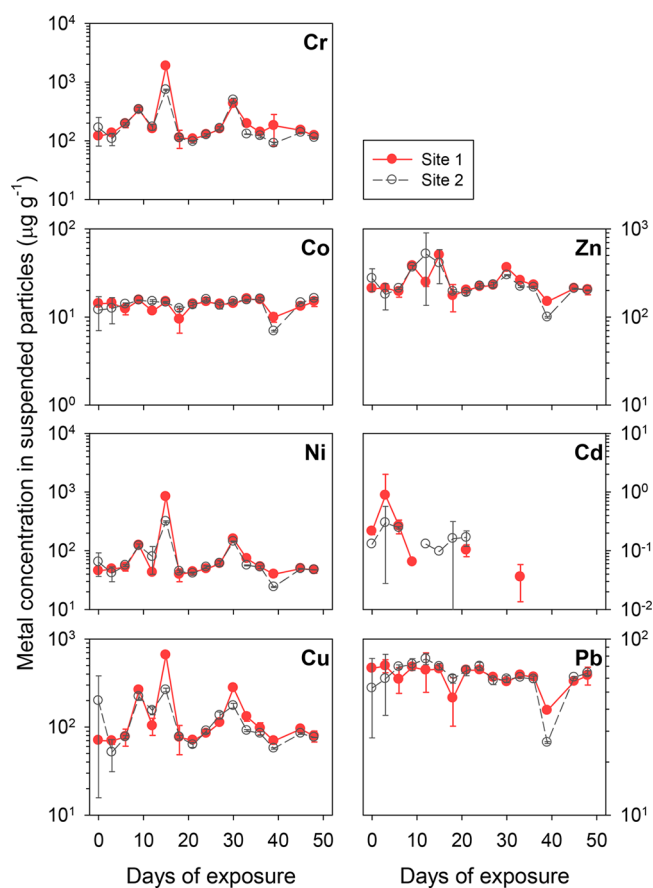
Particulate Metal. The concentrations of metals in suspended particles are summarized in Figure 2. Metal concentrations were similar between the two study sites. The particles also showed elevated concentrations of Cr ($90-1870$ $\mu g\ g^{-1}$; average: 245 $\mu g\ g^{-1}$), Ni ($24-834$ $\mu g\ g^{-1}$; average: 94 $\mu g\ g^{-1}$), Cu ($52-658$ $\mu g\ g^{-1}$; average: 132 $\mu g\ g^{-1}$), and Zn ($99-519$ $\mu g\ g^{-1}$, average: 251 $\mu g\ g^{-1}$) (Table S5), consistent with the measurements in waters. The concentrations of Co and Pb were comparable or slightly higher than those observed in other rivers and estuaries.[14,29,30] Interestingly, Cd concentration in the Jiulong River estuary ($\sim$0.1 $\mu g\ g^{-1}$) was much lower than those observed elsewhere (Table S5). It is similar to the concentrations ($0.04-0.24$ $\mu g\ g^{-1}$) found in intertidal sediments in areas adjacent to Jiulong River estuary,[26] both suggesting low natural background and anthropogenic contamination of Cd in this area.

Jiulong River estuary is a shallow water estuary and usually turbid. Therefore, a large proportion of the sampled suspended particles may be resuspended surface sediments in addition to biotic and organic detritus. Filter-feeding bivalves, including oysters, can select particles with variable efficiency before ingestion, preferring particles of higher nutritional value.[31] Therefore, the sampled particles should not be considered equal in composition to those ingested by the oysters. Nevertheless, metal bioavailability in sediments was found comparable to that in phytoplankton cells. For example, the assimilation efficiencies of Cd (30%−40%), Se (26%−35%), and Zn (34−44%) from sediment particles were only slightly

lower or similar to those observed in phytoplankton cells; sediment particles thus contributed an important fraction to metal bioaccumulation in oysters.[22]

The samples of suspended particles were grab samples taken every 3 days. Although taking samples at 3 day intervals during the 48 day experiment was labor intensive, it was still uncertain whether the samples were representative enough. Considering the dynamic nature of estuarine waters and the complex composition of food ingested by oysters, it is challenging to find a time-efficient and cost-efficient method to measure concentrations of metals in the "real" food of oysters. Taking grab samples like what we did in this study is a matter of expediency.

Metal Accumulation in Oysters and Toxicokinetics. The bioaccumulation of most of the studied metals in the oysters was well described by a simple toxicokinetic model, using metal concentrations in water and suspended particles as driving variables (Figure 3). Large interindividual variations
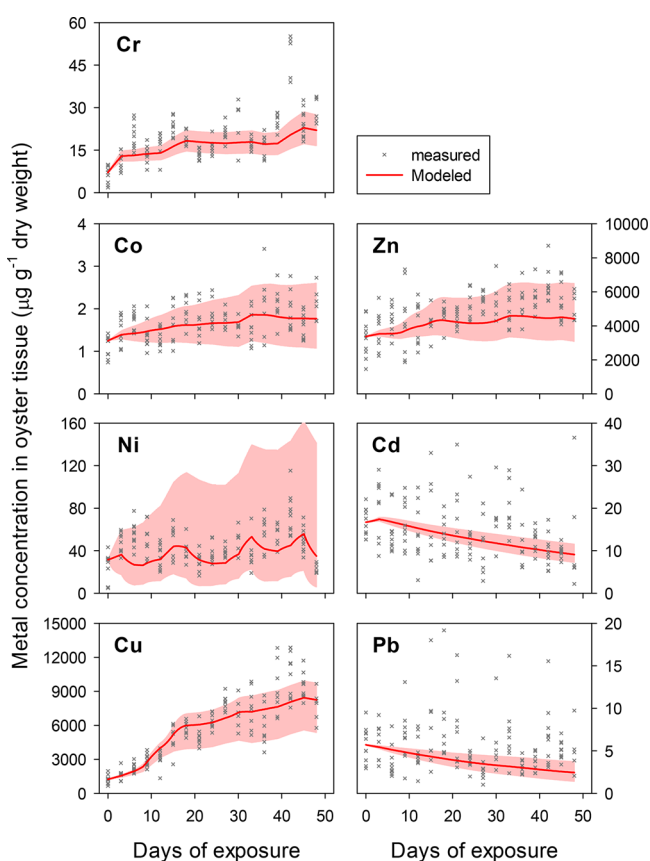
Table 1. Estimated Values of the Toxicokinetic Parameters (k_u, k_f, and k_e)[a]

metal	k_u (L g^{-1} day^{-1})	k_f (g g^{-1} day^{-1})	k_e (day^{-1})
Cr	1.3 ± 0.2	0.000 35 ± 0.000 21	0.0066 ± 0.0012
	(0.9, 1.6)	(0.000 04, 0.000 78)	(0.0044, 0.0087)
Co	0.071 ± 0.035	0.0032 ± 0.0018	0.025 ± 0.017
	(0.011, 0.137)	(0.0003, 0.0074)	(0.002, 0.071)
Ni	0.39 ± 0.23	0.0039 ± 0.0026	0.32 ± 0.18
	(0.07, 0.89)	(0.0006, 0.0100)	(0.05, 0.72)
Cu	6.3 ± 1.9	0.65 ± 0.25	0.0017 ± 0.0014
	(3.8, 10.5)	(0.06, 0.95)	(0.0001, 0.0044)
Zn	5.6 ± 2.2	0.39 ± 0.15	0.012 ± 0.004
	(0.4, 9.2)	(0.15, 0.74)	(0.003, 0.020)
Cd	1.5 ± 0.6	0.16 ± 0.09	0.0074 ± 0.0036
	(0.4, 2.6)	(0.02, 0.31)	(0.0009, 0.0136)
Pb	0.11 ± 0.07	0.0011 ± 0.0006	0.0061 ± 0.0020
	(0.01, 0.25)	(0.0003, 0.0024)	(0.0033, 0.0099)

[a]The values are mean ± standard deviation; values in parentheses are 95% confidence intervals. The statistics summarize the parameter samples generated by the MCMC fittings of the site 1 data (see Figures S7−S13 for more information regarding the parameter samples).

further validated with the results observed at site 2. The time-course of oyster metal concentrations at site 2 was well predicted by the calibrated model (Figure S6), with most of the predictions within a factor of 0.5 to 2 of observed concentrations (Figures 4 and 5).
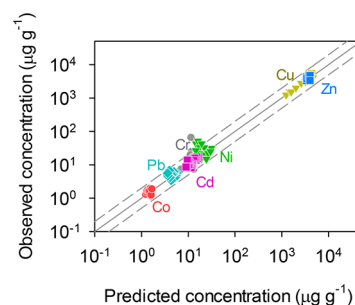

Figure 4. Comparison between observed and model-predicted metal concentrations in oysters at site 2. The observed values are the measured median concentrations of ~10 replicated oysters. The predicted values are the average concentrations predicted by the model based on the parameter samples from the MCMC fittings of data from site 1. The solid line is the curve $y = x$; the two dashed lines are the curves $y = 2 \cdot x$ and $y = x/2$, respectively.

Figure 3. Metal bioaccumulation in soft tissues of oysters at site 1 during the 48 day transplantation. The × symbols represent measured concentrations; the red curves and the shaded areas are average concentrations and 95% confidence intervals predicted by the model based on the parameter samples from the MCMC fittings, respectively. See Figures S7−S13 for the parameter samples.

were observed; therefore, median concentrations were used in the parameter fittings to reduce the possible bias caused by extreme values. The estimated parameter values and confidence intervals are listed in Table 1. The information on parameter samples, including the posterior distribution of parameters and the correlation among parameters, are presented in Figures S7 to S13. Model parameters were calibrated with the bioaccumulation data from site 1, and were

Generally, metals with more obvious bioaccumulation were better simulated with the toxicokinetic model. Increases in the concentrations of Cr, Cu, and Zn were observed in the oysters. Median Cr, Cu, and Zn concentrations increased from 7 to ~20 µg g^{-1}, 1200 to ~9000 µg g^{-1}, and 3400 to ~5000 µg g^{-1}, respectively (Figure 3). The increases of Co and Ni concentrations were less conspicuous; in contrast, slight decreases were observed for Cd and Pb, of which the modeling were relatively poor (Figure 3).

Toxicokinetics. The dissolved uptake rate constants (k_u) were estimated with DGT-labile metal concentrations in this study (Table 1). In principle, they should be higher than k_u values reported in the literature, where k_us were estimated with total dissolved (i.e., filterable) metal concentrations. For example, the k_u of Zn estimated in this study was 5.6 ± 2.2
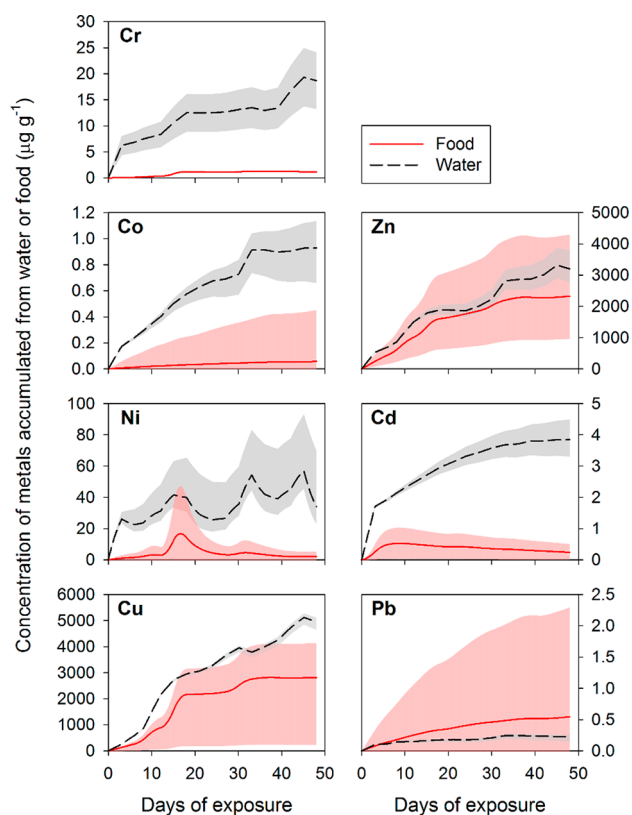
Figure 5. Comparison between water and food (suspended particles) as the source of metals accumulated by the oysters (*C. hongkongensis*) at study site 1 during the 48-d transplant. The curves and the shaded areas are average concentrations and 95% confidence intervals predicted by the model based on the parameter samples from the MCMC fittings of data from site 1.

L g^{-1} day^{-1}. If we assumed a percentage of 28% for DGT-labile Zn to dissolved Zn,[19] the k_u based on dissolved Zn should be 1.6 ± 0.6 L g^{-1} day^{-1}, which was more comparable to those previously measured for the same species of oyster, i.e., 1.15 to 2.40 L g^{-1} day^{-1} measured by Pan and Wang,[23] and 2.05 L g^{-1} day^{-1} by Ke and Wang.[22] Therefore, to use the k_u values estimated in this study, metal concentrations in water should either be measured using DGT probes or judiciously converted from the measurements of other methods.

The dietary assimilation rate constant (k_f) was the product of assimilation efficiency (AE) and the specific ingestion rate (IR), i.e., $k_f = AE \times IR$. The values of AE are metal-, organism-, and food-specific and can be anywhere between 0 and 1 but is often observed between 0.1 to 0.9.[32] The IR for oysters was also highly variable, usually assumed between 0.02 g g^{-1} day^{-1} and 0.6 g g^{-1} day^{-1} based on the laboratory measurements.[22,23] The IR should be rather uncertain especially in dynamic estuarine waters. Therefore, using a simple parameter k_f to relate dietary assimilation proportionately to the metal concentration in food particles is necessarily a simplification. The estimated k_f values were very different between metals (Table 1) and can be as high as 0.65 ± 0.25 g g^{-1} day^{-1} for Cu, suggesting that IR should be no less than 0.65 g g^{-1} day^{-1} on average because $0 \leq AE \leq 1$. Consequently, it can be inferred that the AEs of Cr, Co Ni, and Pb were extremely low, i.e., lower than 1%, which was possibly due to that these metals were mainly refractory species contained in inorganic particles.

The low assimilation efficiency of Cr (0−5%) is already well-known.[32]

The elimination rate constant (k_e) of metals in the oyster was in the order: Ni (0.32 ± 0.18 day^{-1}) > Co (0.025 day^{-1}), Zn (0.012 day^{-1}) > Cd, Cr, Pb, and Cu (0.0017−0.0074 day^{-1}) (Table 1). The k_es of Ni, Zn, and Cd were previously determined for *C. hongkongensis* (see Table S3).[21−23] The k_es in the literature overlap the relatively wide k_e ranges estimated in this study. The k_es of the other metals were not measured in *C. hongkongensis* but in a number of other oysters, using various methods, generating k_es of variable reliability. Not surprisingly, the literature k_e values were scattered and also overlaps the values estimated in this study (Table S3).

For Ni, Co, and Zn, the k_es are higher than or similar to the growth rate constant (g, 0.015−0.018 day^{-1}) of oysters, indicating that the efflux processes played an important role in counteracting metal uptake and controlling tissue concentration of these metals. In contrast, the k_es of Cd, Cr, Pb, and Cu were much lower than g, indicating that growth dilution was the major mechanism in balancing metal bioaccumulation. These four metals were difficult to eliminate once incorporated into oyster tissues.

MCMC Simulation. With MCMC fittings, model parameters were assigned probability distributions instead of the deterministic best-fit values. A parameter sample is a large number (∼10 000 in this study) of combinations of parameter values that can lead to acceptable agreement between model predictions and observations. The parameter samples can thus be considered as posterior distributions of the parameters and are plotted in Figures S7 to S13. Posterior distributions are also summarized by statistics calculated from the parameter samples, including average, standard deviation, and 95% confidence intervals defined by the 2.5th to 97.5th percentiles (Table 1).

Due to the continuously varying water conditions (e.g., salinity, pH, DOC, and temperature) in estuarine waters, the biological variability, and other sources of uncertainty, the model parameters are not expected to be single specific values but rather value distributions. In addition, the parameters may be correlated, either truly correlated or correlated due to the model design. The correlation between parameters cause difficulties in parameter estimation and uncertainty analysis. These are where the MCMC simulations are particularly useful. MCMC fittings yield a joint probability distribution of the model parameters, which describes the simultaneous variation of all parameters and intrinsically considers the correlation between parameters.[25,33] The joint distributions were then used to predict the confidence intervals (shown in Figures 3 and S6) and the relative importance of different pathways in metal bioaccumulation (see below).

Metal Accumulation Pathways. Using parameter samples derived from the MCMC fittings, it is convenient to assess the relative importance (and the associated uncertainties) of water and food as the source of metals for oysters (Figure 5). The bioaccumulation of Cr, Co, Ni, and Cd were clearly dominated by the dissolved phase, whereas Pb might be mainly assimilated from food. For Cu and Zn, both sources were similarly important. The low bioavailability of Cr(III) in food particles was well-documented.[32] In this study, it is possible that the particulate Cr was mainly Cr(III) species contained in mineral particles and thus contributed negligibly to the Cr bioaccumulation. The low contribution of water to the bioaccumulation of Pb is also expected because Pb

concentrations were low in water and high in particles due to the high particle reactivity of Pb.

The quantitative information on the pathways (i.e., water or food) of metal bioaccumulation is crucial for understanding metal biogeochemistry, ecological risks, and biomonitoring data.[34−37] In previous studies, one well-accepted method for delineating the accumulation pathway is modeling. The model parameters (i.e., AE, k_u, and k_e) were first quantified using well-controlled laboratory experiments and were then used in the following calculation in a deterministic way. In this study, we used posterior distributions (from MCMC fittings) instead of fixed values of the model parameter values and provide better uncertainty analysis with more clearly defined confidence intervals (Figure 5).

Model Limitations and Implications. The model parameters were calibrated by exposing oysters to multiple metals in a real estuarine environment. Theoretically, the parameter values obtained in this study are conditional on that very-specific scenario of physicochemical conditions, metal concentrations, particle loads, and so on. Although the model parameters were validated using data collected from another site with good performance (Figure S6), the two sites were rather similar in metal exposure conditions, which weakened the confidence in the predictive power of the calibrated parameters. Nevertheless, the parameter values (with uncertainties) should be more realistic and robust than those calibrated under stable laboratory conditions because they had been averaged over a wide range of exposure conditions in the real estuarine environment. In addition, the MCMC method was intrinsically convenient with regard to incorporating new data input. The parameters can be updated to simulate the new scenario of concern, wherein the parameters values from this study would serve as valuable prior information.

The suspended particles sampled in this study were a mixture of algae, organic detritus and suspended sediment particles, among others, which were not distinguished during metal analysis and modeling. The composition of food particles may have important effects on metal bioavailability to oysters.[38,39] Using a single toxicokinetic parameter (k_f) for modeling metal accumulation from a spectrum of different particles can be considered as a simplification of the complex actual environment and may limit the accuracy of model predictions.

The model can predict the ecological risks associated with metal bioaccumulation (if the bioaccumulation results in adverse effects) and also can be used to back-calculate for setting water quality criteria. For example, the water quality standard (or guideline) of China and Australia on Cd (0.5 and 5 μg L^{-1}) were tested with the model developed in this study, and were found to be not stringent enough for producing oysters safe for human consumption, i.e., with Cd concentration less than 2 μg g^{-1} fresh weight. To produce "safe oysters", the criterion value of Cd needs to be lowered to 0.11 μg L^{-1} (Figure S14).

When interpreting biomonitoring data of dynamic aquatic environments, the toxicokinetic model provides a back-calculation of metal exposure integrated or averaged over a certain timespan before the sampling. One important implication of the toxicokinetic modeling is that for a metal with a longer biological half-life ($t_{1/2} = 0.693/k_e$), the biomonitoring data may reflect its exposure over a longer past period. The average biological half-life estimated for the oyster is in the following order: Ni (2.2 days), Co (28 days),

Zn (58 days), Cd (94 days), Cr (105 days), Pb (114 days), and Cu (408 days). The very short half-life of Ni indicates that Ni concentrations measured in the oysters can only reflect Ni exposure during the past several days, whereas for other metals, the timespan reflected can be months or even longer.

Being kinetic (instead of assuming steady state) is both the strength and weakness of the model. The toxicokinetic model can capture the whole time-course of bioaccumulation rather than simply a steady-state concentration regardless of whether a steady state can be reached. In addition, the toxicokinetic model can deal with fluctuating exposure, which is what happens in real environments, instead of assuming an unrealistic stable exposure. However, calibrating or making full use of the toxicokinetic model demands much more variable input (e.g., metal concentrations in water and food) and, thus, requires more intensive sampling. Although, with the development of automatic in situ or on-site sampling and measurement techniques,[40] collecting data for the toxicokinetic model may become much easier in the future.

In summary, we demonstrated the feasibility of using a simple toxicokinetic model for simulating the bioaccumulation of metals in a complex and dynamic environment. We also introduced the methodology of determining model parameters in the real estuarine environment. Using distributions instead of single values for model parameters make the predictions of the model probabilistic and with clearly defined uncertainties and, thus, particularly useful for risk assessments. Although this study was conducted with one specific oyster species in one specific estuary, the methods we developed can be useful for other biological species and other water bodies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.7b04906.

> Tables showing the settings of initial and prior parameter values, metal toxicokinetics of oysters, and metal concentrations in estuarine waters and suspended particles. Figures showing a map of study sites, oyster growth, salinity and pH data, pair-wise correlation between metal concentrations in water and suspended particles, metal bioaccumulation at site 2, posterior distribution of parameters and correlation among parameters, and Cd bioaccumulation in oysters under hypothetical exposures. Additional information on DGT measurements and model implementation in open-model. (PDF)

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Notes

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■ ACKNOWLEDGMENTS

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Supporting Information

Toxicokinetics of multiple metals in oyster *Crassostrea hongkongensis* determined in the dynamic estuarine environment

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Number of pages: 29

Number of Tables: 5 (Table S1 to Table S5)

Number of Figures: 13 (Figure S1 to Figure S14)

Table S1 Settings of initial parameter values with their distributions and constraints for the least-square fitting. Setting of the values are based on previous studies of metal toxicokinetics in oysters (*see* Table S3).

Metal	k_u (L g^{-1} d^{-1})			k_f (g g^{-1} d^{-1})			k_e (d^{-1})		
	Value	Distribution*	Constraint**	Value	Distribution	Constraint	Value	Distribution	Constraint
Cr	0.1	U(0.01, 1)	(0.01, 1)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)
Co	0.1	U(0.01, 1)	(0.01, 1)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)
Ni	0.1	U(0.01, 1)	(0.01, 1)	0.1	U(0, 1)	(0, 1)	0.1	U(0.01, 0.3)	(0.01, 0.3)
Cu	1	U(0.1, 10)	(0.1, 10)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)
Zn	1	U(0.1, 10)	(0.1, 10)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)
Cd	0.1	U(0.01, 1)	(0.01, 1)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)
Pb	0.1	U(0.01, 1)	(0.01, 1)	0.1	U(0, 1)	(0, 1)	0.01	U(0.001, 0.03)	(0.001, 0.03)

* Uniform distribution (lower bound, upper bound)

** Constraint (lower bound, upper bound)

Table S2 Settings of priori values and distributions of the parameters for the MCMC estimation. The prior values are the best-fit estimates of the least-square fittings.

Distribution: uniform distribution; lower bound = prior value × 0.1; upper bound = prior value × 10.

Constraint: lower bound = prior value × 0.1; upper bound = prior value × 10.

Metal	k_u (L g^{-1} d^{-1})	k_f (g g^{-1} d^{-1})	k_e (d^{-1})
Cr	1.00	0.000426	0.001
Co	0.0670	0.00202	0.0136
Ni	0.278	0.00563	0.230
Cu	7.45	0.111	0.001
Zn	3.13	0.447	0.00673
Cd	0.998	0.0720	0.00342
Pb	0.0536	0.000390	0.001

Table S3 The toxicokinetics of metals in various oyster species reported in literature. The toxicokinetics were determined with the

well-established radiotracer technique in the several studies, of which the results were referred to when setting starting parameter values (listed in

Table S1).

n.a.= not available; a wet weight to dry weight ratio of 8 was assumed for conversion where the results were reported on wet weight basis. *See*

equation (1) in the main text for the meaning of symbols.

* *Crassostrea rivularis* is the same species as *Crassostrea hongkongensis*. For more information, see the study of Wang et al., 2004.

Metal	Oyster species	k_u (L g^{-1} d^{-1})	AE	IR (g g^{-1} d^{-1})	k_f (g g^{-1} d^{-1})	k_e (d^{-1})	Salinity	Temp. (°C)	Reference
	Results below were referred to for setting starting parameter values (listed in Table S1)								
Cd	*Crassostrea hongkongensis*	0.08-0.12	0.48-0.52	0.02-0.2	0.01-0.10	0.011-0.012	25	20	Pan & Wang, 2012
Cd	*Crassostrea rivularis**	0.719	0.40-0.75	0.20-0.60	0.08-0.45	0.014	15	23	Ke & Wang, 2001
Cu	*Saccostrea cucullata*	1.27	0.85	n.a.	n.a.	0.032	20	30	Pan & Wang, 2009
Ni	*Crassostrea hongkongensis*	0.036	0.28	n.a.	n.a.	0.038-0.155	12	20	Yin, 2017 (Mphil thesis)
Zn	*Crassostrea hongkongensis*	1.15-2.40	0.50-0.71	0.02-0.2	0.01-0.10	0.006-0.014	25	20	Pan & Wang, 2012
Zn	*Crassostrea rivularis**	2.05	0.40-0.80	0.20-0.60	0.08-0.48	0.034	15	23	Ke & Wang, 2001
	Results below were not used for setting starting parameter values but are compiled here for comparison								
Ag	*Isognomon isognomon*	0.970	n.a.	n.a.	n.a.	0.00044-0.012	25	36	Hédouin et al., 2010a
Ag	*Malleus regula*	0.226	n.a.	n.a.	n.a.	0.0076-0.021	25	36	Hédouin et al., 2010a
Ag	*Crassostrea virginica*	n.a.	0.44	n.a.	n.a.	0-0.01	28	18	Reinfelder et al., 1997
Cd	*Crassostrea gigas*	~1	n.a.	n.a.	n.a.	n.a.	15	15	Strady et al., 2011
Cd	*Crassostrea gigas*	0.68-9.59	0.08-0.64	n.a.	n.a.	0.011-0.024	26	20-22	Ng et al., 2010
Cd	*Isognomon isognomon*	0.378	n.a.	n.a.	n.a.	0.00018-0.012	25	36	Hédouin et al., 2010a

Metal	Oyster species	k_u (L g^{-1} d^{-1})	AE	IR (g g^{-1} d^{-1})	k_f (g g^{-1} d^{-1})	k_e (d^{-1})	Salinity	Temp. (℃)	Reference
Cd	*Malleus regula*	0.284	n.a.	n.a.	n.a.	0.0007-0.014	25	36	Hédouin et al., 2010a
Cd	*Saccostrea cucullata*	0.343	0.3	0.45	n.a.	n.a.	20	28	Blackmore & Wang, 2004
Cd	*Crassostrea gigas*	0.038-0.056	n.a.	n.a.	n.a.	0.0014-0.0035	37	17	Boisson et al., 2003
Cd	*Crassostrea gigas*	n.a.	n.a.	n.a.	n.a.	0.0051	27-35	n.a.	Geffard et al., 2002
Cd	*Saccostrea glomerata*	0.534	0.30-0.70	0.20-0.60	0.06-0.42	0.004	30	23	Ke & Wang, 2001
Cd	*Crassostrea iredalei*	0.6	n.a.	n.a.	n.a.	0.050	n.a.	n.a.	Lim et al., 1998
Cd	*Crassostrea virginica*	n.a.	0.69	n.a.	n.a.	0-0.01	28	18	Reinfelder et al., 1997
Cd	*Crassostrea gigas*	0.090	n.a.	n.a.	n.a.	n.a.	33	10	Frazier & George, 1983
Cd	*Ostrea edulis*	0.027-0.041	n.a.	n.a.	n.a.	n.a.	33	10	Frazier & George, 1983
Co	*Isognomon isognomon*	0.271	n.a.	n.a.	n.a.	0.009-0.020	25	36	Hédouin et al., 2010a
Co	*Malleus regula*	0.213	n.a.	n.a.	n.a.	0.0094-0.016	25	36	Hédouin et al., 2010a
Co	*Isognomon isognomon*	n.a.	0.15-0.20	n.a.	n.a.	0.027-0.054	25	36	Hédouin et al., 2010b
Co	*Isognomon isognomon*	n.a.	0.21-0.55	n.a.	n.a.	0.026-0.050	25	36	Hédouin et al., 2010b
Co	*Crassostrea virginica*	n.a.	0.34	n.a.	n.a.	0.080	28	18	Reinfelder et al., 1997
Cr	*Isognomon isognomon*	0.083	n.a.	n.a.	n.a.	0.008-0.012	25	36	Hédouin et al., 2010a
Cr	*Malleus regula*	0.066	n.a.	n.a.	n.a.	0.00033-0.011	25	36	Hédouin et al., 2010a
Cu	*Crassostrea gigas*	n.a.	n.a.	n.a.	n.a.	0.0016	27-35	n.a.	Geffard et al., 2002
Cu	*Crassostrea iredalei*	4.712	n.a.	n.a.	n.a.	0.064	n.a.	n.a.	Lim et al., 1998
Cu	*Crassostrea belcheri*	0.22-0.35	n.a.	n.a.	n.a.	0-0.009	10-30	n.a.	Lim et al., 1995
Cu	*Crassostrea gigas*	n.a.	n.a.	n.a.	n.a.	0.028-0.059	30	n.a.	Han et al., 1993
Cu	*Crassostrea cucullata*	0.12-0.60	n.a.	n.a.	n.a.	0.0075	n.a.	n.a.	Silva & Qasim, 1979
Hg(II)	*Saccostrea cucullata*	2.064	0.3	0.45	n.a.	n.a.	20	28	Blackmore & Wang, 2004
MeHg	*Saccostrea cucullata*	3.445	0.9	0.45	n.a.	n.a.	20	28	Blackmore & Wang, 2004
Mn	*Isognomon isognomon*	n.a.	0.2-0.9	n.a.	n.a.	0.010-0.028	25	36	Hédouin et al., 2010b
Pb	*Crassostrea iredalei*	1.096	n.a.	n.a.	n.a.	0.058	n.a.	n.a.	Lim et al., 1998

Metal	Oyster species	k_u (L g^{-1} d^{-1})	AE	IR (g g^{-1} d^{-1})	k_f (g g^{-1} d^{-1})	k_e (d^{-1})	Salinity	Temp. (°C)	Reference
Se	*Crassostrea rivularis*	0.06	0.25-0.75	0.20-0.60	0.05-0.45	0.014	15	23	Ke & Wang, 2001
Se	*Saccostrea glomerata*	0.064	0.35-0.70	0.20-0.60	0.07-0.42	0.013	30	23	Ke & Wang, 2001
Se	*Crassostrea virginica*	n.a.	0.7	n.a.	n.a.	0.070	28	18	Reinfelder et al., 1997
Zn	*Isognomon isognomon*	0.826	n.a.	n.a.	n.a.	0.00036-0.0095	25	36	Hédouin et al., 2010a
Zn	*Malleus regula*	0.784	n.a.	n.a.	n.a.	0.00082-0.012	25	36	Hédouin et al., 2010a
Zn	*Isognomon isognomon*	n.a.	0.51-0.76	n.a.	n.a.	0.0002-0.015	25	36	Hédouin et al., 2010b
Zn	*Saccostrea cucullata*	0.745	0.5	0.45	n.a.	n.a.	20	28	Blackmore & Wang, 2004
Zn	*Crassostrea gigas*	n.a.	n.a.	n.a.	n.a.	0.0021	27-35	n.a.	Geffard et al., 2002
Zn	*Saccostrea glomerata*	1.206	0.30-0.60	0.20-0.60	0.06-0.36	0.003	30	23	Ke & Wang, 2001
Zn	*Crassostrea iredalei*	96	n.a.	n.a.	n.a.	0.042	n.a.	n.a.	Lim et al., 1998
Zn	*Crassostrea virginica*	n.a.	0.73	n.a.	n.a.	0-0.01	28	18	Reinfelder et al., 1997
Zn	*Crassostrea gigas*	n.a.	n.a.	n.a.	n.a.	0.023-0.042	30	n.a.	Han et al., 1993

Table S4 Comparison of metal concentrations ($\mu g\ L^{-1}$) in water measured in the present study and those reported in the literature and the ambient water quality standards and criteria.

Estuarine waters, criteria/standards	Cr	Co	Ni	Cu	Zn	Cd	Pb	Comments
Jiulong River estuary, site 1	0.54 ± 0.43	0.54 ± 0.23	31 ± 15	24 ± 12	16 ± 8	0.089 ± 0.065	0.10 ± 0.08	DGT measured concentrations; this study
Jiulong River estuary, site 2	0.30 ± 0.28	0.44 ± 0.22	16 ± 7	9.1 ± 5.8	10 ± 7	0.076 ± 0.020	0.12 ± 0.14	
Jiulong River estuary	2-18	—	7-57	1-18	2-27	—	0.01-0.32	0.2-µm filterable concentrations; Wang and Wang, 2016
Jiuzhen Harbour, Zhangzhou, China	0.28	0.16	1.18	0.37	2.90	0.02	0.036	DGT measured concentrations; Weng and Wang, 2014
Jiulong River estuary, Baijiao site	3.67	0.43	14.6	9.26	9.76	0.07	0.13	
Seven estuaries in Britain contaminated by industrial and mining activities	—	—	0.81-9.4	1.2-10	1.9-22	0.018-0.220	0.170-1.10	Dissolved concentrations; compiled by Luoma and Rainbow (2008), pp. 72.
Restronguet Creek in Britain (receives acid mine drainage)	—	—	18	176	20460	38	4	
Hudson River estuary in USA	—	—	4.5	3.5-4.5	10-17	0.25-0.30	—	
Sea Water Quality Standard of China (GB 3097-1997)	50[a]	—	5	5	20	1	1	Standard Class I, marine fishery waters, marine natural reserves
Sea Water Quality Standard of China (GB 3097-1997)	100[b]	—	10	10	50	5	5	Standard Class II, aquaculture areas, beach, sports or entertainment areas, industrial water related to food production
US National Recommended Aquatic Life Criteria	50[c]	—	8.2	3.1	81	7.9	8.1	Saltwater Criterion Continuous Concentration (chronic criteria)
Australian and New Zealand Guidelines for Fresh and Marine Water Quality	20	—	100	5	5	0.5-5	1-7	Toxicant guidelines for the protection of aquaculture species

[a] Standard for total Cr; the standard for Cr(VI) is 5 $\mu g\ L^{-1}$.

[b] Standard for total Cr; the standard for Cr(VI) is 10 $\mu g\ L^{-1}$.

[c] Criteria for Cr(VI).

Table S5 Comparison of metal concentrations (µg g^{-1} dry weight) in suspended particles of estuaries and rivers.

Estuary / river	Cr	Co	Ni	Cu	Zn	Cd	Pb	Comments
Jiulong River estuary, site 1	284 ± 433 (107–1870)	14 ± 2 (9–16)	110 ± 196 (39–834)	146 ± 151 (70–658)	249 ± 91 (150–504)	0.10 ± 0.22 (0.00–0.88)	61 ± 8 (39–70)	This study; values are mean ± sd and range.
Jiulong River estuary, site 2	207 ± 177 (90–742)	14 ± 2 (7–16)	78 ± 70 (24–314)	119 ± 65 (52–264)	253 ± 102 (99–519)	0.08 ± 0.10 (0.00–0.30)	61 ± 11 (26–77)	
Jiulong River estuary, Baijiao site	90 (38–188)	12 (7–35)	31 (21–40)	55 (24–103)	146 (98–215)	0.12 (0.06–0.18)	49 (18–58)	Weng and Wang, 2014; values are mean and range.
Jiuzhen Harbour, Zhangzhou, China	53 (26–87)	6.2 (2.6–8.7)	22 (18–32)	27 (18–44)	128 (79–195)	0.14 (0.17–0.22)	45 (24–66)	
Sabine estuary, Texas, USA	—	—	—	20	80	—	20	Benoit et al., 1994; average concentrations estimated from Fig.4 & 5 therein.
Galveston estuary, Texas, USA	—	—	—	20	50	—	12	
Major rivers around the world	—	—	30–105	30–74	—	0.3–6.0	23–46	Elbaz-Poulichet et al., 1996; the major rivers include Amazon, Changjiang, Huanghe, Mississippi, Orinoco, Lena, Rhône, and Ebro.
World river average	—	—	90	100	—	1.2	35	
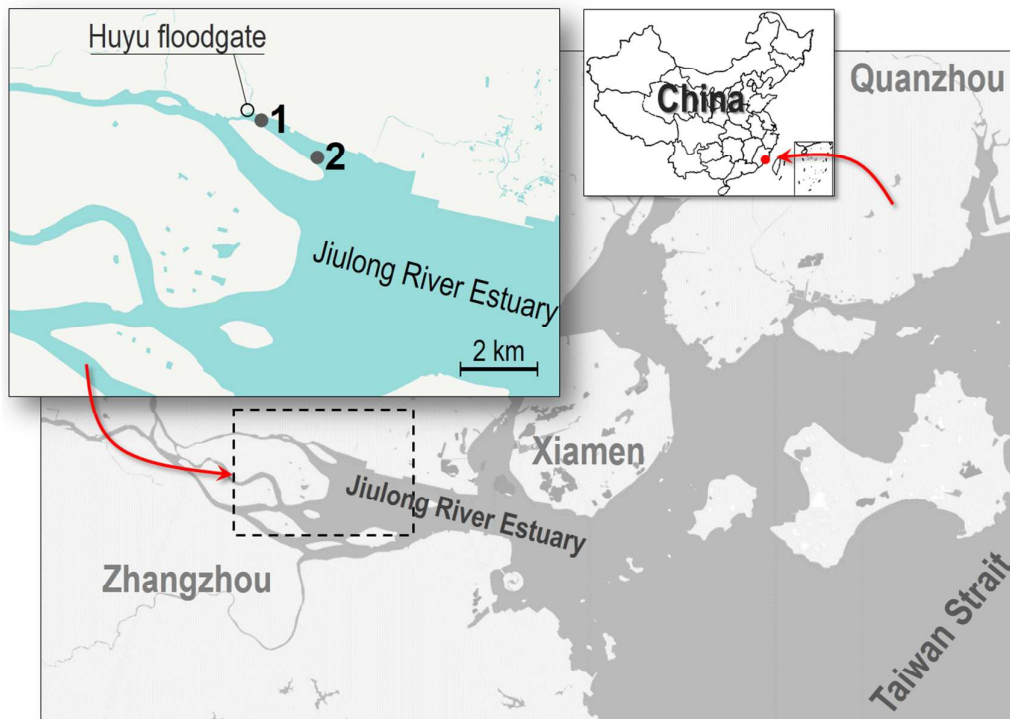
Figure S1 The two sites in Jiulong River estuary for oyster transplant. Site 1 (24°28′38.64″N, 117°55′1.62″E) was directly affected by the effluent discharged from Huyu floodgate; site 2 (24°27′59.42″N，117°55′50.00″E) was approximately 2 km lower stream.
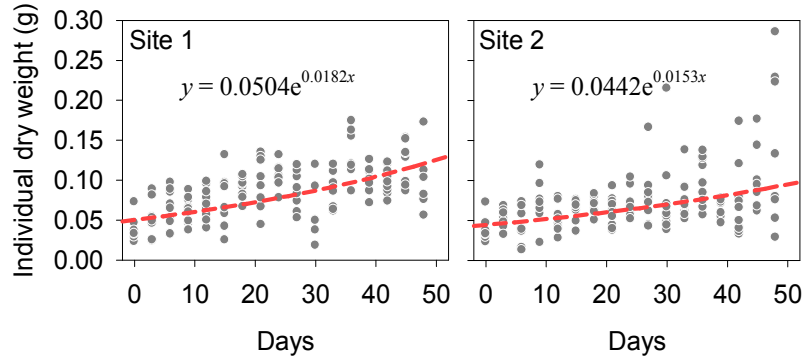
Figure S2 The increases of individual dry weight of oysters during the 48-d transplant at the two study sites.

Site 1: $y = (0.0504 \pm 0.0026) \cdot e^{(0.0182 \pm 0.0025) \cdot x}$;

Site 2: $y = (0.0442 \pm 0.0023) \cdot e^{(0.0153 \pm 0.0023) \cdot x}$.
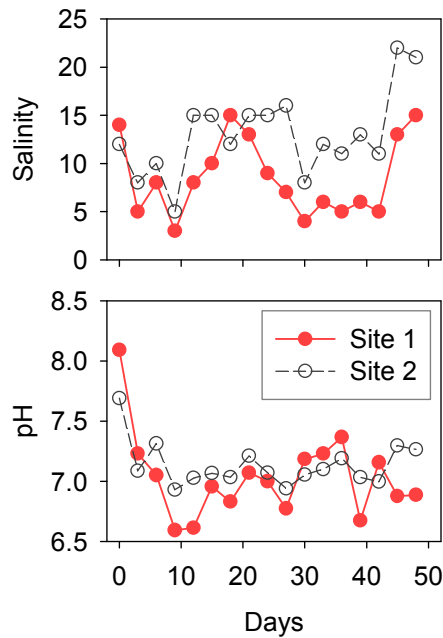
Figure S3 Salinity and pH of water at the two study sites during the 48-d transplant experiment.
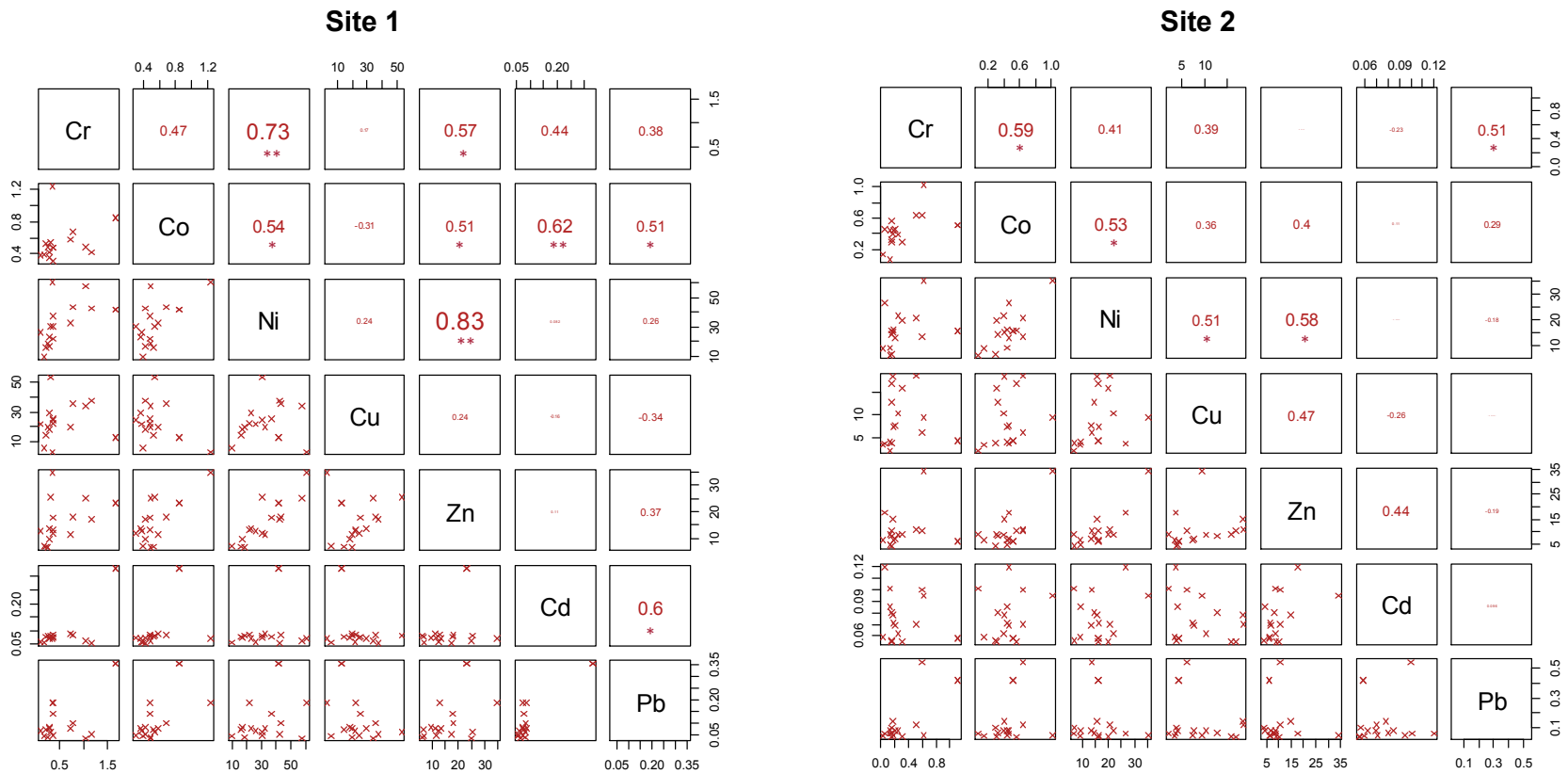
Figure S4 The pairwise correlation between metal concentrations in water measured by <u>DGT</u> probes at the two study sites.

Lower triangle: scatter plots; upper triangle: Spearman correlation coefficients (*$p < 0.05$; **$p < 0.01$).
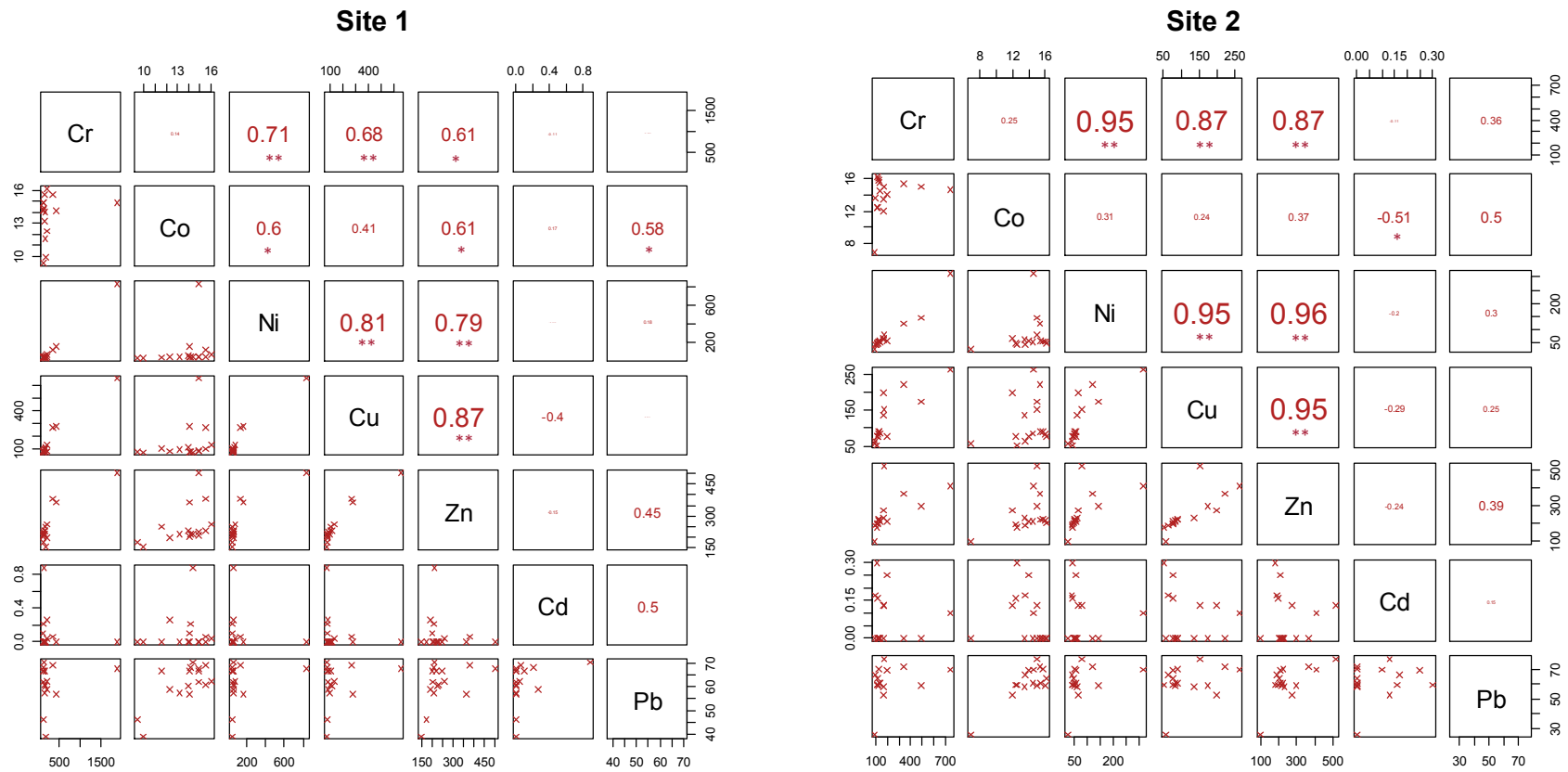
Figure S5 The pairwise correlation between metal concentrations in <u>suspended particles</u> at the two study sites.

Lower triangle: scatter plots; upper triangle: Spearman correlation coefficients (*$p < 0.05$; **$p < 0.01$).
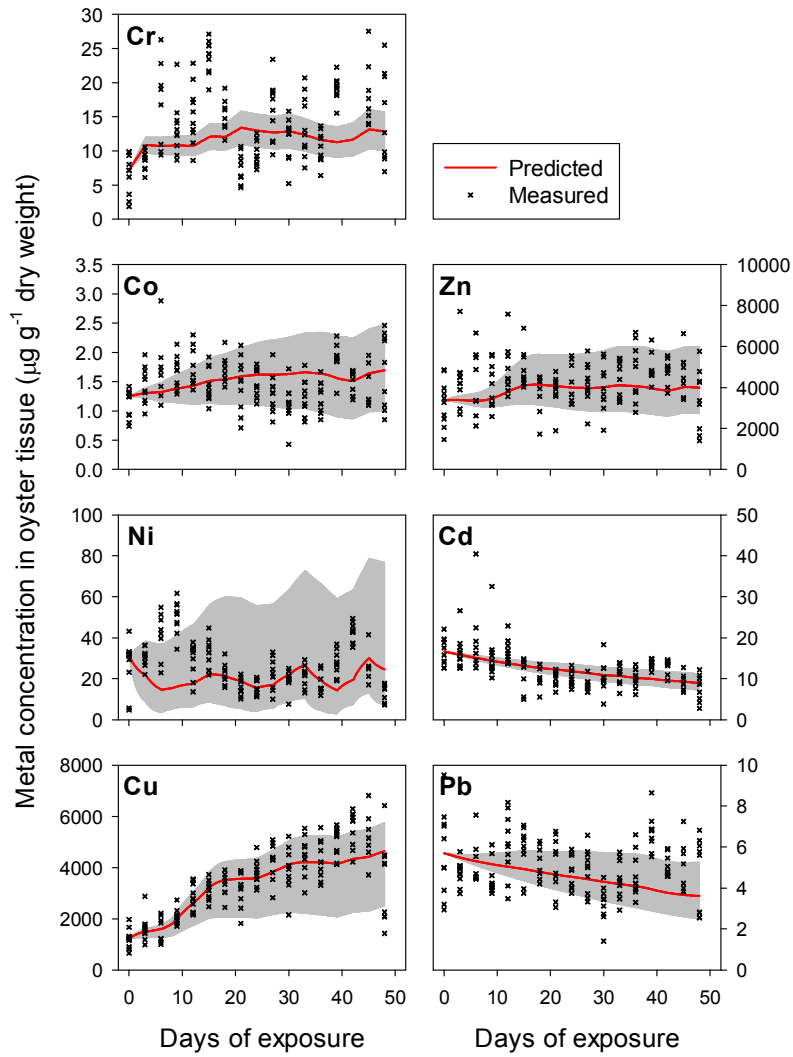
Figure S6 Metal accumulation in soft tissue of oysters at <u>site 2</u> during the 48-d transplant. The × symbols represent measured values; the red curves are model predicted values; the shaded areas are 95% confidence intervals of prediction. The values of model parameters used for the predictions were calibrated using data from <u>site 1</u>.
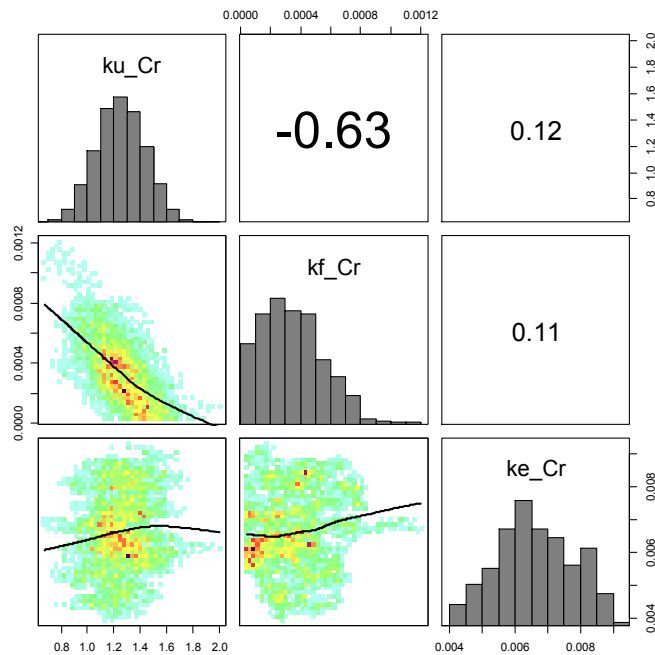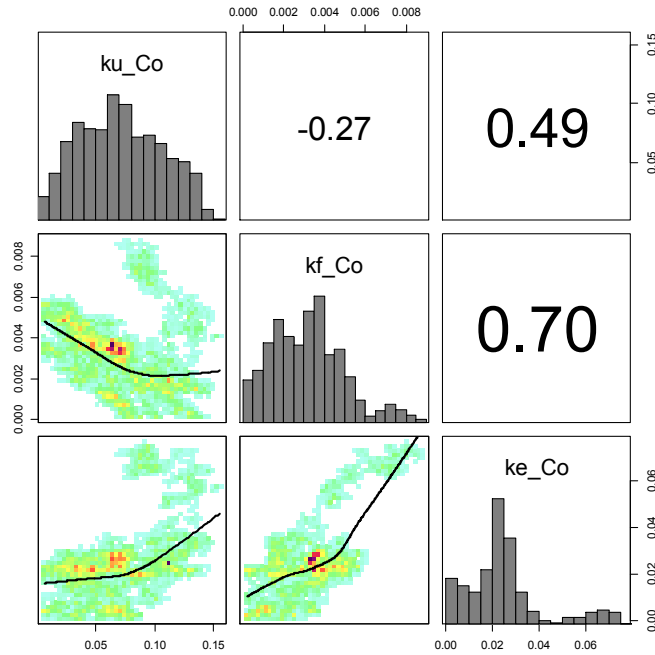
Figure S7 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Cr</u> and the associated correlation among the parameters. The parameter values presented here are from the parameter sample generated by the MCMC fitting and are the first 10000 skipped values (skip interval = 2) after 50% burn in. The probability distributions of k_u, k_f, and k_e are in the diagonal of the matrix. Plots in the lower triangle are scatter plots showing pairwise correlation of the three parameters, with the color indicating the probability density (red to blue = high to low). Values in the upper triangle are the Pearson correlation coefficients.

Figure S8 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Co</u> and the associated correlation among the parameters. Others *see* Fig. S5.
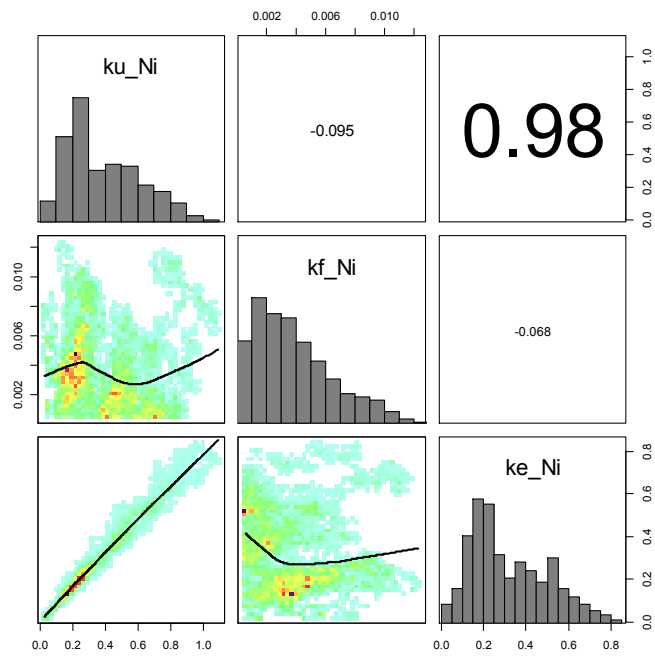

Figure S9 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Ni</u> and the associated correlation among the parameters. Others *see* Fig. S5.
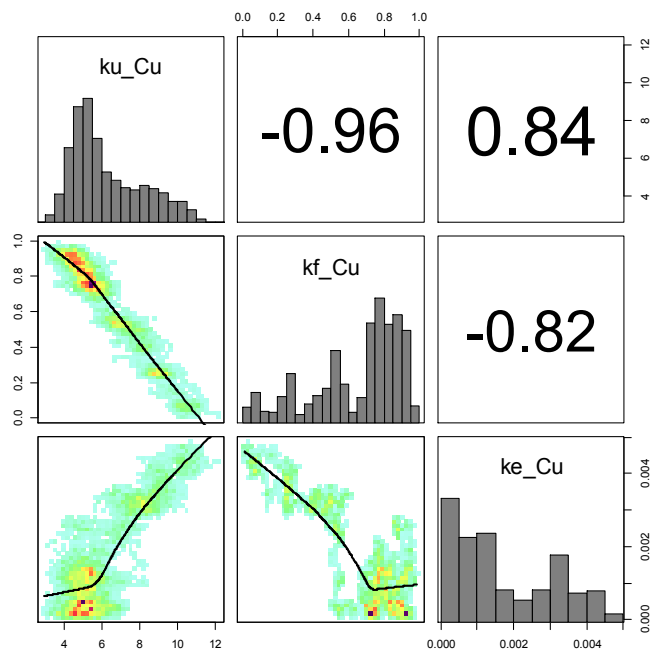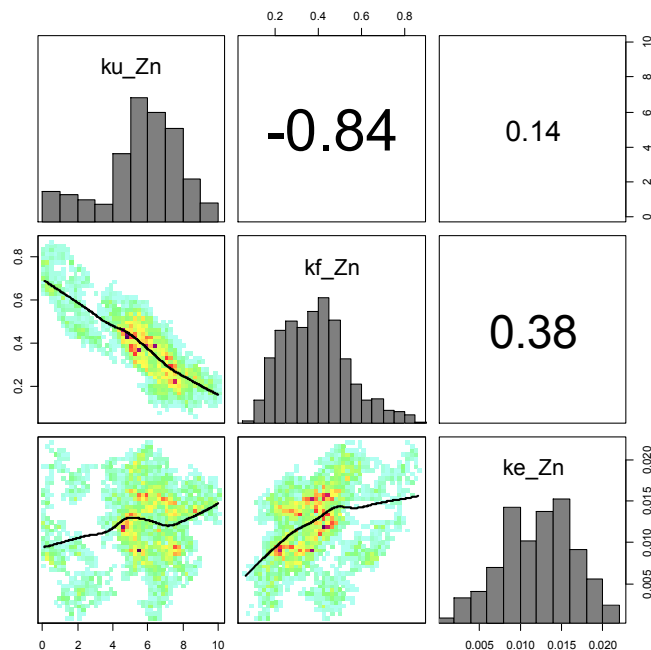
Figure S10 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Cu</u> and the associated correlation among the parameters. Others *see* Fig. S5.

Figure S11 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Zn</u> and the associated correlation among the parameters. Others *see* Fig. S5.
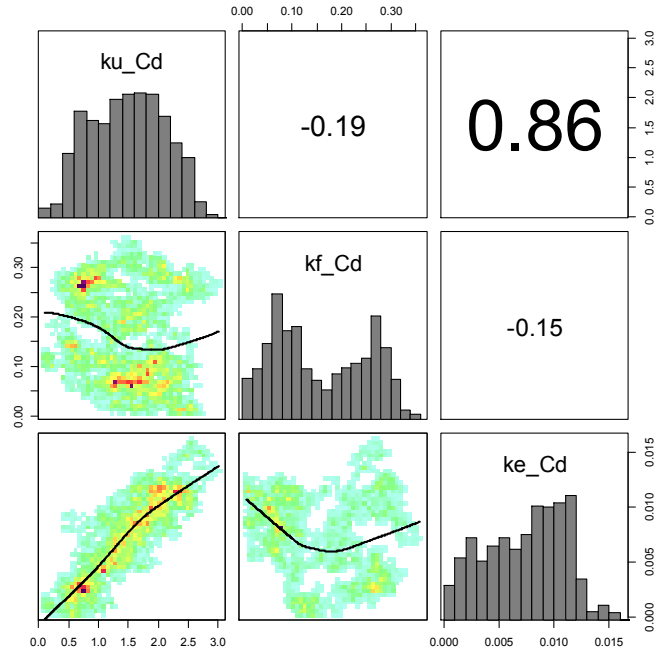
Figure S12 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Cd</u> and the associated correlation among the parameters. Others *see* Fig. S5.
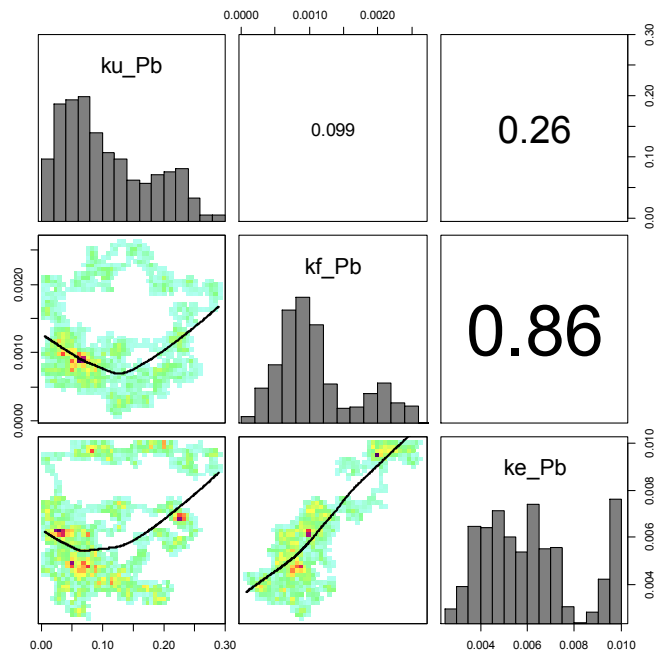

Figure S13 The posterior distribution of the toxicokinetic parameters (k_u, k_f, k_e) of <u>Pb</u> and the associated correlation among the parameters. Others *see* Fig. S5.
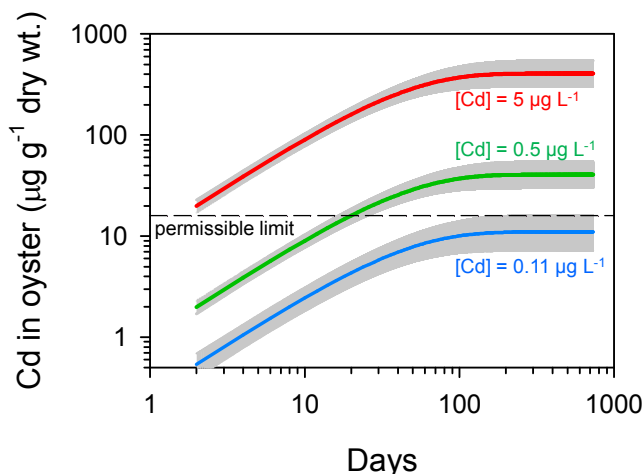
Figure S14 The simulated Cd bioaccumulation in the oyster *C. hongkongensis* living in estuarine waters with Cd concentration at 0.11 µg L^{-1}, 0.5 µg L^{-1}, and 5 µg L^{-1}. The solid curves are predicted average concentrations; the shaded areas are predicted 95% confidence intervals.

The predictions were made using the Cd parameter samples generated in this study (*see* Fig. S12). The Cd concentration of 5 µg L^{-1} is the class II standard of "Sea Water Quality Standard of China" (GB 3097-1997), which is applicable to waters for aquaculture; Cd concentration of 0.5 µg L^{-1} is from "Australian and New Zealand Guidelines for Fresh and Marine Water Quality" for the protection of aquaculture species. The proportion of DGT-labile Cd is assumed to be 100% of dissolved Cd (Munksgaard and Parry, 2003). The Cd K_d of 1800 L kg^{-1} was assumed based on the study of Weng and Wang (2014). The steady-state Cd concentration reached in the oyster tissues under both scenarios would exceed the maximum permissible limit for Cd in bivalves of China (GB 2762—2012), i.e., 2 µg g^{-1} fresh weight or 16 µg g^{-1} dry weight (assuming a conversion factor of 8), suggesting that the current standards or guidelines are not protective enough for producing oysters considered safe for human consumption. For producing safe oyster (i.e., 95% of the oysters having tissue Cd ≤ 16 µg g^{-1}), the criteria value needs to be set at 0.11 µg L^{-1}.

DGT-labile metal concentration

A DGT unit is composed of three layers, including the outer layer of a 0.45 μm pore size polysulfone filter, the middle layer of diffusive gel, and the bottom layer of gel embedded with chelex resin. The metal species that can bind to chelex resin are accumulated in the bottom layer and measured by the technique. The DGT measured metal species are considered labile and potentially bioavailable. Metal concentrations measured by DGT (μg L^{-1}) were calculated according to the following equation:

$$C_{\mathrm{DGT}} = \frac{M \cdot \Delta g}{D \cdot A \cdot t}$$

where M (ng) is the mass of metal concentrated by the chelex gel; Δg (cm) is the total thickness of the diffusive layer (0.08 cm) and the outer filter layer (0.014 cm); D (cm^2 s^{-1}) is the diffusion coefficient of each metal at the average temperature over the deployment period; A (3.14 cm^2) is the area of the contact between the DGT probe and the ambient water; t (s) is the duration of DGT deployment. See more information in the document "Practical Guide for Using DGT in Waters" available at the website of DGT Research Ltd.: www.dgtresearch.com.

Model implementation in openmodel

Below we use the case of Cu as an example to show how to implement the toxicokinetic model in the software openmodel (version 2.4.2). The information needed for model implementation are provided, including model equations, differential equation initial values, input data, and settings of initial parameter values. Default settings of the software were used for parameter estimations, except that 20000 (instead of 10000) iterations were used in the Metropolis-Hastings estimation. For further information on how to define "merit function", how to conduct "parameter estimation", how to view and evaluate "parameter sample", and so on can be found in the document "OpenModel User Guide" accompanying the software. The model file (*.OMMLX format) can be provided on request (via email: tanqg@xmu.edu.cn). The software is developed by Neil Crout at the University of Nottingham and can be downloaded at the website: http://openmodel.info/

Main code

```
Cw_Cu=water_S1.DGT_Cu(t)
Cf_Cu=particle_S1.SS_Cu(t)
Cint_Cu.rate=(ku_Cu*Cw_Cu+kf_Cu*Cf_Cu)-(ke_Cu+g)*Cint_Cu
FromFood_Cu.rate=kf_Cu*Cf_Cu-(ke_Cu+g)*FromFood_Cu
FromWater_Cu.rate=ku_Cu*Cw_Cu-(ke_Cu+g)*FromWater_Cu
```

Main code - view in the openmodel interface

```
Symbols  Initial   Main

    1  Cw_Cu=water_S1.DGT_Cu(t)
    2  Cf_Cu=particle_S1.SS_Cu(t)
    3  Cint_Cu.rate=(ku_Cu*Cw_Cu+kf_Cu*Cf_Cu)-(ke_Cu+g)*Cint_Cu
    4  FromFood_Cu.rate=kf_Cu*Cf_Cu-(ke_Cu+g)*FromFood_Cu
    5  FromWater_Cu.rate=ku_Cu*Cw_Cu-(ke_Cu+g)*FromWater_Cu
```

Differential equation initial values - view in the openmodel interface

```
Symbols  Initial   Main

    1  //median Cu concentration on day 0
    2  Cint_Cu=1234
```

Defining the symbols - view in the openmodel interface

```
Symbols  Initial   Main

  Add    Remove  Rename   Trace

 ▲ ⬛ Module1              Description:
   ▲ ✕ Variables
      ✕ Cf_Cu
      ✕ Cw_Cu             Units:
   ▲ ⬛ ODEs
      ⬛ Cint_Cu
      ⬛ FromFood_Cu       Information:
      ⬛ FromWater_Cu
   ▲ ⬛ Parameters
      ⬛ g
      ⬛ ke_Cu
      ⬛ kf_Cu
      ⬛ ku_Cu
```

Data sheet "`water_S1`" (DGT measured metal concentrations at site 1)

day	DGT_Cr	DGT_Co	DGT_Ni	DGT_Cu	DGT_Zn	DGT_Cd	DGT_Pb
0	1.66	0.85	41.84	12.87	23.15	0.330	0.356
3	1.66	0.85	41.84	12.87	23.15	0.330	0.356
3.1	0.30	0.42	16.72	18.26	9.81	0.073	0.081
6	0.30	0.42	16.72	18.26	9.81	0.073	0.081
6.1	0.38	0.48	21.83	22.16	13.16	0.086	0.187
8	0.38	0.48	21.83	22.16	13.16	0.086	0.187
8.1	0.33	0.54	30.51	53.01	25.49	0.082	0.060
12	0.33	0.54	30.51	53.01	25.49	0.082	0.060
12.1	0.79	0.68	43.38	35.29	18.11	0.084	0.098
15	0.79	0.68	43.38	35.29	18.11	0.084	0.098
15.1	0.73	0.58	32.55	19.89	11.37	0.088	0.076
18	0.73	0.58	32.55	19.89	11.37	0.088	0.076
18.1	0.23	0.53	15.91	14.37	6.87	0.078	0.072
21	0.23	0.53	15.91	14.37	6.87	0.078	0.072
21.1	0.26	0.49	18.69	20.21	6.58	0.082	0.038
24	0.26	0.49	18.69	20.21	6.58	0.082	0.038
24.1	0.29	0.36	22.87	29.11	13.67	0.072	0.076
27	0.29	0.36	22.87	29.11	13.67	0.072	0.076
27.1	0.37	0.48	37.12	25.55	17.77	0.078	0.139
30	0.37	0.48	37.12	25.55	17.77	0.078	0.139
30.1	0.36	1.24	60.60	3.31	34.63	0.072	0.185
33	0.36	1.24	60.60	3.31	34.63	0.072	0.185
33.1	0.12	0.38	26.00	21.87	12.72	0.059	0.067
36	0.12	0.38	26.00	21.87	12.72	0.059	0.067
36.1	0.38	0.31	30.50	24.70	11.75	0.073	0.047
39	0.38	0.31	30.50	24.70	11.75	0.073	0.047
39.1	1.17	0.42	42.49	37.46	17.32	0.055	0.051
42	1.17	0.42	42.49	37.46	17.32	0.055	0.051
42.1	1.04	0.49	57.75	33.78	25.02	0.063	0.033
45	1.04	0.49	57.75	33.78	25.02	0.063	0.033
45.1	0.19	0.39	9.66	5.97	7.16	0.056	0.043
48	0.19	0.39	9.66	5.97	7.16	0.056	0.043

Data sheet `"water_S1"` - view in the openmodel interface

day	DGT_Cr	DGT_Co	DGT_Ni	DGT_Cu	DGT_Zn	DGT_Cd	DGT_Pb
0	1.662	0.8462	41.8421	12.874	23.1465	0.3301	0.3562
3	1.662	0.8462	41.8421	12.874	23.1465	0.3301	0.3562
3.1	0.3	0.4232	16.717	18.2563	9.8106	0.0726	0.0809
6	0.3	0.4232	16.717	18.2563	9.8106	0.0726	0.0809
6.1	0.3834	0.48	21.8271	22.1634	13.16	0.0856	0.1867
8	0.3834	0.48	21.8271	22.1634	13.16	0.0856	0.1867
8.1	0.326	0.5408	30.5117	53.0107	25.4857	0.0817	0.0596
12	0.326	0.5408	30.5117	53.0107	25.4857	0.0817	0.0596
12.1	0.7913	0.6825	43.3833	35.286	18.1072	0.0843	0.0984
15	0.7913	0.6825	43.3833	35.286	18.1072	0.0843	0.0984
15.1	0.7261	0.5781	32.5549	19.8859	11.3653	0.0878	0.0756
18	0.7261	0.5781	32.5549	19.8859	11.3653	0.0878	0.0756
18.1	0.2277	0.525	15.9053	14.3739	6.8697	0.078	0.0715
21	0.2277	0.525	15.9053	14.3739	6.8697	0.078	0.0715
21.1	0.257	0.4904	18.6912	20.2116	6.579	0.0822	0.0375
24	0.257	0.4904	18.6912	20.2116	6.579	0.0822	0.0375
24.1	0.2881	0.3641	22.8673	29.1084	13.6659	0.0721	0.0761
27	0.2881	0.3641	22.8673	29.1084	13.6659	0.0721	0.0761
27.1	0.374	0.4827	37.1225	25.5509	17.769	0.0783	0.1392
30	0.374	0.4827	37.1225	25.5509	17.769	0.0783	0.1392
30.1	0.3575	1.2389	60.6	3.3112	34.6299	0.0722	0.1852
33	0.3575	1.2389	60.6	3.3112	34.6299	0.0722	0.1852
33.1	0.1179	0.3808	25.9969	21.8724	12.7239	0.059	0.0665
36	0.1179	0.3808	25.9969	21.8724	12.7239	0.059	0.0665
36.1	0.383	0.3124	30.4986	24.6976	11.7528	0.0734	0.0474
39	0.383	0.3124	30.4986	24.6976	11.7528	0.0734	0.0474
39.1	1.17	0.417	42.4921	37.4551	17.3241	0.0547	0.0511
42	1.17	0.417	42.4921	37.4551	17.3241	0.0547	0.0511
42.1	1.041	0.4931	57.745	33.78	25.0181	0.0631	0.033
45	1.041	0.4931	57.745	33.78	25.0181	0.0631	0.033
45.1	0.1894	0.3906	9.6554	5.9654	7.156	0.0561	0.043
48	0.1894	0.3906	9.6554	5.9654	7.156	0.0561	0.043

Tree navigation (left panel):
- Cu bioaccumulation
  - Modules
  - Parameterisations
  - Data Sheets
    - oyster_median_S1
    - water_S1
      - day
      - DGT_Cr
      - DGT_Co
      - DGT_Ni
      - DGT_Cu
      - DGT_Zn
      - DGT_Cd
      - DGT_Pb
    - particle_S1
    - oyster_all_S1
  - Grids

Buttons: Paste | Load from column file... | Copy

Data sheet "`particle_S1`" (metal concentrations in suspended particles at site 1)

day	SS_Cr	SS_Co	SS_Ni	SS_Cu	SS_Zn	SS_Cd	SS_Pb
0	119	14.2	45.4	70.2	210	0.21	68.2
3	135	14.4	48.6	69.5	213	0.88	70.3
6	196	12.3	52.6	77.6	194	0.26	59.0
9	339	15.6	123.2	263.6	380	0.06	69.2
12	160	11.6	42.6	103.2	247	0.00	66.6
15	1874	14.9	834.5	657.9	504	0.00	67.5
18	112	9.4	39.5	76.5	174	0.00	46.1
21	107	14.1	43.6	70.7	201	0.10	66.5
24	127	14.9	49.0	84.6	221	0.00	66.6
27	158	14.0	60.2	112.0	228	0.00	60.5
30	429	14.1	158.2	278.9	364	0.00	57.1
33	195	16.1	73.0	131.0	259	0.04	62.4
36	140	15.6	53.0	96.7	230	0.00	60.9
39	182	9.9	39.7	69.5	150	0.00	39.2
45	151	13.2	49.5	94.8	211	0.00	57.4
48	122	14.9	47.0	79.0	204	0.00	62.0

Data sheet "`particle_S1`" - view in the openmodel interface

Data sheet "oyster_median_S1" (median metal concentrations in oysters at site 1)

day	Cr	Co	Ni	Cu	Zn	Cd	Pb
0	7.2	1.25	31.5	1234	3374	16.7	5.7
3	9.7	1.61	48.0	1705	4120	21.5	6.9
6	18.7	1.77	53.4	2177	4402	13.3	2.9
9	13.6	1.31	50.9	2786	4031	15.4	6.9
12	18.8	1.34	36.8	3257	4835	11.9	4.3
15	23.4	1.70	55.9	4837	4322	18.7	6.4
18	18.4	1.91	40.6	5774	4807	13.4	6.3
21	13.4	1.54	27.8	4733	4532	14.4	7.2
24	15.7	1.81	34.7	6301	5090	12.6	4.0
27	20.8	1.66	38.1	8049	5558	10.3	2.6
30	29.1	1.60	52.3	6974	5294	17.4	4.8
33	16.9	1.56	35.6	7440	4828	17.8	6.6
36	17.8	2.23	61.0	5539	5290	9.7	3.3
39	25.5	2.09	59.5	8661	5674	13.3	3.8
42	57.9	1.70	74.8	10964	6206	9.4	6.5
45	23.9	1.66	49.9	9232	5190	9.8	5.1
48	30.0	2.12	22.0	8050	5133	6.4	5.0

Data sheet "oyster_median_S1" - view in the openmodel interface

Specifying starting parameter values - view in the openmodel interface

Parameter Values	Covariance				
Symbol	Value	Distribution	Constraint	User Distribution	User Constraint
g	0.018	default	default		
ke_Cu	0.01	user defin	user defin	uniform: lower=0.001 (absolute); upper=0.03 (absolute)	Lower=0.001 (absolute);Upper=0.03 (absolute);
kf_Cu	0.1	user defin	user defin	uniform: lower=0 (absolute); upper=1 (absolute)	Lower=0 (absolute);Upper=1 (absolute);
ku_Cu	1	user defin	user defin	uniform: lower=0.1 (factor); upper=10 (factor)	Lower=0.1 (factor); Upper=10 (factor)

See Table S1 and S2 for more information on the settings of parameter values.

Settings for the Metropolis-Hastings estimation - view in the openmodel interface

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